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Chapter 5

An Integrated Approach to Iron Deficiency Anemia

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Abstract

Iron deficiency is a common nutritional disorder in developing countries and contributes significantly to reduced work productivity and economic output as well as to increased morbidity and mortality. There are well-established biochemical tests for assessing iron status in developed countries. However, cost and interference from infectious conditions make it difficult to assess iron status in many developing country settings. Examination of the hemoglobin distribution in the population and assessment of the hemoglobin response to supplementation are alternative approaches to define iron status and the nature of anemia. Prevention and control of iron deficiency requires the combined approach of dietary improvement, fortification of a common staple food when feasible, and appropriate iron supplementation for infants and pregnant women. In all these intervention activities, operational research is needed to improve effectiveness. In addition, controlling iron deficiency requires coordination with other nutrition and primary health care programs as part of an integrated approach to improved health and nutrition of the population. A randomized, controlled double-blind clinical trial was conducted to compare the efficacy and safety of herbal medicinal treatment syrup Sharbat-a-Folad versus syrup Ferplex for the treatment of iron deficiency anemia (IDA).

Keywords: iron deficiency, herbal medicine, anemia

1. Introduction

Iron deficiency anemia (IDA) is the most common nutritional deficiency worldwide. It can cause reduced work capacity in adults [1] and impact motor and mental development in children and adolescents [2]. There is some evidence that iron deficiency without anemia affects cognition in adolescent girls [3] and causes fatigue in adult women [4]. IDA may affect visual and auditory functioning and is weakly associated with poor cognitive development in children.

The term "anemia" is used for a group of conditions in which the number of red blood cells in the blood is lower than normal, or the red blood cells do not have enough hemoglobin. The estimates of the prevalence of anemia vary widely and accurate data are often lacking, and it can be assumed that significant proportions of young children and women of childbearing age are anemic [5, 6].

Iron deficiency results when iron demand by the body is not met by iron absorption from the diet. Thus, patients with IDA presenting in primary care may have inadequate dietary intake, hampered absorption, or physiologic losses in a woman of reproductive age. It also could be a sign of blood loss, known or occult. IDA is never an end diagnosis; the work-up is not complete until the reason for IDA is known.

The risk factors associated with IDA includes the following: low socioeconomic status, race as black women have a lower mean hemoglobin and a wider standard deviation than white women, inadequate dietary intake or parity, suggesting that there may be an unidentified, possibly racial factor predisposing these women to iron deficiency [7].

Anemia cannot be reliably diagnosed by clinical presentation. Fatigue, the most common reason to check hemoglobin, was caused by anemia in only one out of 52 patients in a primary care practice [8]. In a hospital setting, pallor predicted anemia with a likelihood ratio (LR) of 4.5. However, the absence of pallor was less helpful in ruling out anemia, giving an LR of 0.6 even when anemia was defined as less than 9 g per dL (90 g per L), a lower diagnostic level than that of the World Health Organization (WHO) or the Centers for Disease Control and Prevention (CDC) [9]. Other classic symptoms such as koilonychia (spoon nails), glossitis, or dysphagia are not common in the developed world [10].

The diagnosis of IDA requires that a patient be anemic and show laboratory evidence of iron deficiency. Red blood cells in IDA are usually described as being microcytic (i.e., mean corpuscular volume less than 80 μm^3 [80 fL]) and hypochromic; however, the manifestation of iron deficiency occurs in several stages [11]. Patients with a serum ferritin concentration less than 25 ng per mL (25 mcg per L) have a very high probability of being iron deficient. The most accurate initial diagnostic test for IDA is the serum ferritin measurement. Serum ferritin values greater than 100 ng per mL (100 mcg per L) indicate adequate iron stores and a low likelihood ratio of IDA [12]. In some populations, such as those with inflammatory disease or cirrhosis, these tests must be interpreted slightly differently because ferritin is an acute-phase reactant. Cutoffs for abnormality in these patients generally are higher [13].

Another laboratory change that occurs in patients with IDA is an increase in the iron-carrying protein transferrin. The amount of iron available to bind to this molecule is reduced, causing a decrease in the transferrin saturation and an increase in the total iron-binding capacity. The serum transferrin receptor assay is a newer approach to measuring iron status at the cellular level. Increased levels are found in patients with IDA, and normal levels are found in patients with anemia of chronic disease [14].

The treatment arms were chosen by block randomization in batches of eight using computer-generated random numbers to assign women to one of the four combinations of trial intervention. Block randomization was chosen to ensure that the experimental groups would not

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become unbalanced if the rate of recruitment at sites differed greatly. A research fellow with no other role in the project is overseeing the labeling and packing of all the trial medications and holding the randomization schedule until the code is broken.

1.1. Level of significance

This is the set standard to decide the cutoff value between treatment groups when comparing the two groups. If the results are significant at this set level ($\alpha = 0.05$), the null hypothesis will be rejected.

2. Patients, materials, and methods

2.1. Study design

The study was based on an experimental, randomized double-blind clinical trial. The study had been conducted according to principles of good clinical practice (i.e., an informed consent was obtained before enrollment and proper history and clinical examination were recorded on each follow-up), and the study was carried out during May 2003 to June 2004. A randomized double-blind experimental design was employed to test the hypotheses; therefore, by manipulating the independent variables (efficacy, side effects), any effects on dependent variable (herbal and allopathic treatment) could be monitored.

2.2. Patients

The study was conducted on 50 patients aged 12–40 years who were attending gynecological outpatient visits in Shifa-ul-Mulk Memorial Hospital.

2.3. Setting

The study was conducted in the Department of Gynecology and Obstetrics at Shifa-ul-Mulk Memorial Hospital for Eastern Medicine at Hamdard University in Karachi.

2.4. Sample selection

In this study, only the patients selectively enrolled were diagnosed with IDA through clinical history and laboratory investigations were enrolled. Diagnosis of IDA was based on the typical signs and symptoms and laboratory finding. Complete blood picture (CBC), hemoglobin, erythrocyte sedimentation rate (ESR), and urine (routine and microscopic) tests were also performed.

Recruiting GPs identify eligible women in their clinical practice and invite them to consider participation in the trial, after provision of sufficient information to make an informed decision. Women who meet the eligibility criteria and agree to participate are required to give written informed consent. Recruiting GPs also obtain demographic and relevant past and current medical data, particularly data relevant to risk factors for developing iron deficiency anemia. The interventions being tested are as follows:

(i) Control group received allopathic treatment (syrup Ferplex two teaspoons for seven days), (ii) and the test group received the herbal medicine (two teaspoons of syrup Foulad for seven days). All participants were observed for three follow-up visits over the course of treatment until they improved.

Blood samples were collected for CBC when the clinical picture shows the complete improvement to access the efficacy of the trial and confirmation and improvement in hemoglobin status. Same parameters were followed in control group.

2.5. Assessment

The normal hemoglobin count in reference to age set standard of WHO, blood morphology, was used as the primary outcome of the study. Secondary outcomes included the total symptoms score, the global assessment of the treatment by the investigator, and the women safety of the drugs and severity of adverse events at each follow-up visit. The relationship of each event to the study drug was also assessed. The safety outcome measure was the incidence of treatment-emergent adverse events in both groups. A blood specimen for routine CBC was obtained prior to the treatment.

2.6. Inclusion criteria

Persons may be included in the trial, if they meet the following criteria:

- Female patients between the aged of 12–40 years suffering from IDA.
- All socioeconomical classes were included.
- Verbal consent and willingness to participate in all scheduled study visits and tests.
- Patients suffering from IDA.
- Patients living in Karachi, Pakistan.

2.7. Exclusion criteria

Patients were excluded, if they have any of the following criteria:

- Patients having other associated pathologies such as uncontrolled diabetes, hypertension, liver disorders, etc.
- Patients having other types of anemia such as protein deficiency anemia, pernicious anemia, sickle cell anemia, and thalassaemia.
- Known cases of iron therapy failure.
- Patients suffering from iron deficiency in secondary to malignancies.
- Patient belonging to any area outside Karachi because of intrinsic difficulty to follow up.

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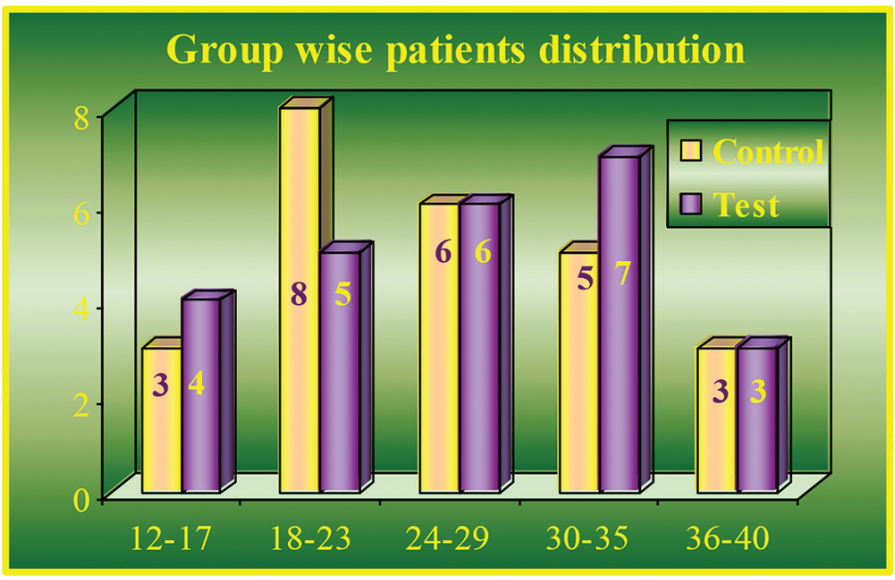
3. Results

The present study is to investigate formulated herbal medicine syrup Foulad for the treatment of IDA. The clinical screening of hematopoietic activity between Foulad and Ferplex was carried out to determine the efficacy and side effects towards off this malaise. These evaluations were based on clinical and laboratory findings so as to ascertain the rate of improvement in hemoglobin. In this study, a total of 50 patients were initially randomized and screened, the intent-to-treat population enrolled. The patients were evenly distributed to test or control group with the ratio of 1:1, that is, 25 in each group. This loss was distributed evenly between the treatment groups. The demographic and baseline characteristics of the intent-to-treat group were comparable for the herbal medicine and allopathic medicine treatment.

3.1. Patient characteristics

There were no significant differences in the mean age (26.12 ± 7.92 vs. 26.48 ± 4.75 test and control group, respectively, (**Table 1**) values between the treatment groups at the start of the clinical trial. All the patients were distributed in five-class interval ranging from age 12 to 40 years. The mean age of the married women's was 32.0 versus 32.46 and mean age of the single patients was 19.75 versus 20.0.



Marital status	Treatment group	Mean	Number (*n*)	Standard deviation	Sum
Married	Control	32.46	13	4.75	422
	Test	32.00	13	4.98	416
	Total	32.23	26	4.78	838

Marital status	Treatment group	Mean	Number (*n*)	Standard deviation	Sum
Single	Control	20.00	12	3.86	240
	Test	19.75	12	5.17	237
	Total	19.88	24	4.47	477
Total	Control	26.48	25	7.65	662
	Test	26.12	25	7.98	653
	Total	26.30	50	7.74	1315

Table 1. Marital status by treatment group.

3.2. Treatment assignment and follow-up

All subjects were clinically studied and completed assigned therapy during the period May 2001 to June 2004. Results presented below represent an intention-to-treat analysis, as stipulated by this study protocol. Baseline patient characteristics for all study variables were balanced among treatment groups (**Table 2**).

Anemia history and examination at baseline		Treatment group		Total *n* = 50	*p*value
		Control	Test		
Severity of anemia	Mild	10	7	17	0.650
	Moderate	12	15	27	
	Severe	3	3	6	
Symptoms of anemia	Asymptomatic	5	2	7	0.613
	Fatigue	2	5	7	
	Reduced concentration	0	1	1	
	Loss of appetite	3	1	4	
	Pica	1	2	3	
Signs of anemia	Koilonychia	1	1	2	
	Brittle nails	1	0	1	
	Pallor	9	11	20	
	Tachycardia	3	2	5	
Causes of anemia	Blood loss	14	13	27	0.990
	Decreased iron utilization	6	7	13	
	Dietary inadequacy	4	4	8	
	Malabsorption	1	1	2	

Table 2. Baseline demographic variables.

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3.3. Baseline demographic variables

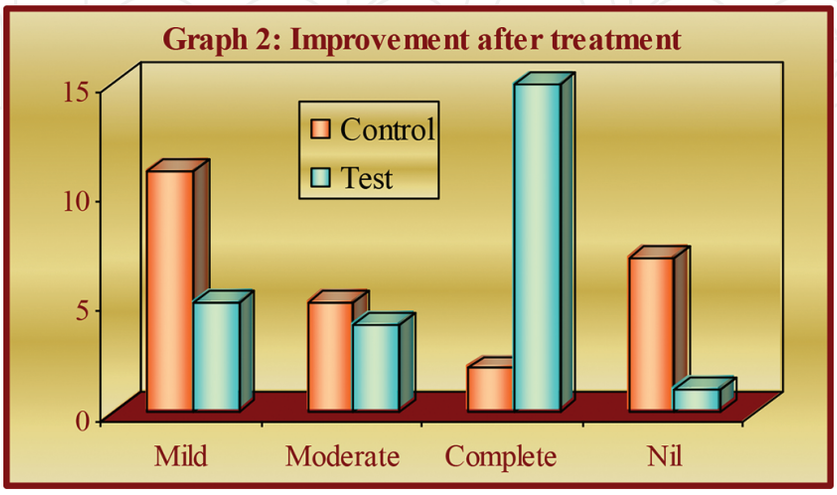
The baseline pretreatment analyses of IDA history and examination were performed. The clinical evaluation proforma of IDA was filled at the time of enrollment in both treatment groups. Patient's baseline demographic variables for IDA history and general physical examination were summarized for each treatment group. As depicted in **Table 2**, patient characteristics were equally balanced between the test and control groups. The two treatment groups did not differ significantly (all $p < 0.05$) from each other at any time point. The most common IDA symptom was pallor 44.0% in allopathic treated and 36.0% in herbal-treated patients. Whereas the common cause of IDA noted in this trial was the blood loss 56% in allopathic treated and 52% in herbal-treated patients.

3.4. Baseline severity of anemia

The assessment of severity of IDA at the time of enrollment exhibited following results test group versus control group, mild anemia 7 patients (28%) versus 10 (40%), moderate anemia 15 patients (60%) versus 12 (48%), severe anemia 3 patients (12%) versus 3 (12%) patients noticed in the both treatment groups. Baseline severity of anemia did not differ between the two groups. Comparative analysis of the baseline data using chi-square test confirms that there were no baseline differences among the treatment group as evident from p values in **Table 2**.

3.5. Effects of therapy on hemoglobin status

Hemoglobin increased dramatically in both treatment groups after therapy (as dissipated in graph 2). The rates of the improvement in hemoglobin concentration were higher in the herbal treatment group at all times after treatment and it revealed that the efficacy of herbal treatment is as superior to allopathic treatment ($p = 0.001$). The total duration of treatment was 4 weeks in both treatment groups. The clinical success rates on the basis of self-assessment of patient regression of complaints and physician examination on follow-up were more effective in test group (as in graph 2).



Clinical failures or no significant improvement in hemoglobin after treatment occurred in 1/25 patients (4%) receiving herbal medicine and in 7/25 patients (28%) receiving allopathic medicines (graph 2). Clinical success rates for those with mild-to-moderate infections and those with severe infections were higher in test treatment group. For the overall, clinical success was observed in 15/25 patients (60%) of cases in herbal-treated patients and in 2/25 (8%) of cases in allopathic-treated patients.

The overall evaluation was mainly based on the efficacy of drugs in reducing anemia in terms of both objective and subjective symptoms. The syrup Foulad produced a better result than allopathic medicines, which showed an overall cure rate of 60% versus 8% significantly effective as confirmed by chi-square test and the test treatment has superior efficacy than control treatment ($p = 0.001$).

3.6. Safety evaluations

All the patients enrolled in the study were evaluated for safety. Adverse effects observed after administration of medicine are summarized in **Table 3**. The majority of adverse events were assessed as mild in severity. Adverse events categorized by the physician (researcher) as possibly or definitely drug related were reported in 3/25 patients (12%) receiving herbal medicine and in 15/25 patients (60%) given allopathic medicine.

Observed Side effects	Treatment group		Total	*p* value
	Control	Test		
Constipation	2	1	3	0.010
Diarrhea	3	1	4	
Nausea	9	1	10	
Vomiting	1	0	1	
No complaints	10	22	32	
Total patients	25	25	5	

Table 3. Side effects on patient's self-assessment.

Nausea was the most common drug-related events among allopathic medicine (36%) and herbal group (4%) recipients. Overall side effects ($p = 0.010$) were greater in control-treated participants than in test participants. No severe or serious adverse side effects were observed that interfere with activities of daily living. Comparison of data recorded by participants relating to these variables showed highly significant differences between test and control groups for measurements side effects as shown in **Table 3**.

Consequently, the generated data rejected the null hypothesis (when $p < 0.05$); hence, the null hypothesis was rejected on the basis of statistical findings in regard to efficacy and safety.

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4. Discussion

Iron deficiency anemia (IDA) is most often a polysymptomatic disease. The use of allopathic drug combination has been considered as one of the effective therapy. But this is not feasible, as besides being cost prohibitive, they are not without side effects. The herbal formulation syrup Foulad contains herbs, which are known for its wide range of clinical use in indigenous medicine. It has been proved that these herbs exert profound activity for the improvement of hemoglobin percentage.

This unicenter trial demonstrated that herbal medicine was more effective in the management of patients with IDA. Herbal treatment resulted in a 60% clinical cure or improvement rate, which is superior to that achieved with allopathic therapy 8% clinical success rate. The response rate of hemoglobin improvement status before and after treatment suggests that syrup Foulad has the higher efficacy as allopathic medicine ($p > 0.001$).

In light of study that the authors have presented, it is concluded that phytomedicine administered under a randomized double-blind trial is exhibiting desirable effects with a profound margin of safety. The plus point is that the formulations are absolutely cost-effective and have shown promising results even in surveillance studies. The spectrum of herbal medicine has been widening following the modalities of integrated medicine like our eastern system of medicine.

The medicinal word is switching over to alternative medicine, including herbal medicine especially South Asia, due to its tremendous potential that is being confirmed by current researches. In this unicenter study, syrup Foulad was well tolerated and had a rate of drug-related adverse events less than to that of patients treated with syrup Ferplex ($p = 0.010$). Mild nausea was the most commonly reported adverse events in test treatment groups and control group.

5. Conclusion

Based on the statistical result of present clinical trial, it can be concluded that

- a comparative evaluation of the IDA treatment by Sharbat Foulad vis-a-vis the syrup Ferplex differs in treatment response, the herbal medicine is superior to allopathic medication.
- there was less untoward manifestation associated with the use of syrup Foulad and this is found a good acceptability by most of the treated patients. Syrup Foulad has added the benefit of safety.

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